## Morbidity and Mortality Events Committees

The Morbidity and Mortality Events Committee will review all primary endpoints that occur in the MADIT-CRT study. Their decisions are based on independent physician review of the data. Two endpoint subcommittees have been established to independently review information on endpoint events: HF Events Review Committee and Mortality Events Review Committee

**HF Events Review Committee:** HF Events will be documented by clinical data from the hospital or out-subject record in English, the official language of the study. The defining clinical criteria will be distributed to the enrolling center personnel prior to study initiation. Classification of cause and circumstances surrounding the HF Event will occur upon agreement of the reviewers.

In MADIT-CRT, we will categorize a subject as having a "Heart Failure Event" when the subject has symptoms and/or signs consistent with congestive heart failure and:

- **receives intravenous decongestive therapy (IV diuretics, IV neseritide, IV inotropes)**, that does not involve formal in-patient hospital admission, regardless of the setting (i.e. in an emergency room setting, in the physician's office, etc.), **or**
- **receives an augmented heart failure regimen with oral or intravenous medications during an in-hospital stay** (formal hospital admission is defined as admission to hospital that includes a calendar date change).

Members of the Heart Failure Events Review Committee are:

Dwyer, Edward, MD (chair)
Retired
Tenafly, NJ

Kukin, Marrick, MD
Director, Heart Failure Program
St. Luke's-Roosevelt Hospitals
New York, NY

Lichstein, Edgar, MD
Maimonides Medical Center
Brooklyn, NY

# Heart Failure Event Committee Operating Manual

**Purpose:**
To outline the procedures to be followed by the Heart Failure Event end-point Committee (HFEC) for the adjudication of heart failure events in the MADIT-CRT trial.

**Scope:**
Definition of a heart failure event; committee composition; preparation of data for committee adjudication; adjudication procedures; and documentation of adjudication.
Determination of heart failure events and classification of hospitalizations; Study Heart Failure Event case report forms; endpoint documentation and data flow. Definition of hospitalizations.

**A. Definition of Heart Failure Event**
In MADIT-CRT, subjects will be categorized as having a "heart failure event" when the subject has symptoms and/or signs consistent with new or worsening congestive heart failure and:

1. **receives intravenous decongestive therapy (IV diuretics, IV neseritide, IV inotropes)**, that does not involve formal in-patient hospital admission, regardless of the setting (i.e. in an emergency room setting, in the physician's office, etc.), **or**
2. **receives an augmented heart failure regimen with oral or intravenous medications during an in-hospital stay** (formal hospital admission is defined as admission to hospital that includes a calendar date change).

**Congestive heart failure diagnosis**: There is no diagnostic test for heart failure, since it is largely a clinical diagnosis that is based upon a careful history and physical examination. The committee will consider the following worsening or new symptoms as consistent with congestive heart failure:

- dyspnea with exertion or at rest
- orthopnea
- paroxysmal nocturnal dyspnea
- fatigue

Supporting evidence will be required by at least one physical finding, such as:

- increasing edema
- pulmonary rales
- a new S3 gallop
- elevation of the jugular venous pressure
- hepatomegaly
- ascites

Other supporting objective data that may be used by the committee would include, but not limited to:

- decreased oxygen saturation (< 91%)
- chest X-ray evidence of increasing alveolar congestion or vascular redistribution
- a documented increase of 10 mmHg in the pulmonary capillary pressure
- BNP>150 pg/mL

The committee will also take into account as supporting evidence, the response of the symptoms, signs and test data to decongestion therapy. Cardiogenic shock will not qualify as worsening congestive heart failure unless the above described supporting criteria are also present.

**B. Committee Composition**

The MADIT-CRT Heart Failure Event Endpoint Committee (HFEC) will consist of, at a minimum, three non-participating cardiologists and a cardiac RN. One of the cardiologists specializes in heart failure, while the other two are non-invasive, general cardiologists. The RN has work background in the CCU, Catheterization laboratory and the Electrophysiology Laboratory. The nurse will be responsible for reviewing non-cardiovascular hospitalizations for the purpose of determining that no cardiovascular event was the cause of admission and that no findings suggestive of heart failure are present. The committee will be responsible for the adjudication of the occurrence of heart failure events in the MADIT-CRT clinical trial within 30 days of CDC providing sufficient supporting documentation. The purpose of this process is to provide maximum uniformity and continuity in the review and categorization of heart failure events, while still maintaining latitude for professional judgment by the investigators and committee members. In the event that future additions to the committee would be considered necessary, additions will be purposely made to ensure that the committee will always be composed of an odd number of cardiologist members.

The Committee members are the following:
Edward M. Dwyer M.D. NJ Medical School/UMDNJ, Newark, NJ., Chairman
Edgar Lichstein M.D. Maimonides Medical Center, Brooklyn, NY
Marrick Kukin M.D., St. Lukes/Roosevelt Hospital, New York, NY
Patricia Dwyer RN, St. Lukes/Roosevelt Hospital, New York, NY

**C. Preparation of data for Committee adjudication**

The Coordination and Data Center (CDC) will collect, prepare, and ensure that all data will come to the committee without subject identification or any descriptions of device implantation. The CDC will also compile and forward to the HFEC the following data for all potential heart failure events and all other hospitalizations:

**Heart Failure Event (hospitalization) Supporting Documentation**
Form 17A

Form 18A (completion of the narrative summary required)
Discharge Summary
* Initial History and Physical exam
* Chest X-Ray report from time most proximate to the heart failure event
Form 3A
Form 5A and B (last one completed prior to the event)
Form 30A
Other supporting documents as requested by the committee on a case-by-case basis.
* Highly desirable but not obligatory for completion of supporting documentation

**Heart Failure Event (out-patient) Supporting Documentation**
Form 18A (completion of the narrative summary required)
Out-patient physician description and nurse notes (if available) that document the heart failure event
* Chest X-Ray report. Only an X-ray within 48 hours of the heart failure event should be included.
If available, a follow up visit physician description of treatment response.
Form 3A
Form 5A and B (last one completed prior to the event)
Form 21A
Other supporting documents as requested by the committee on a case-by-case basis.
* Highly desirable but not obligatory for completion of supporting documentation

**Hospitalization supporting documents**
17A (completion of the narrative summary required)
Discharge Summary
* Initial History and physical exam
Other supporting documents as requested by the committee on a case-by-case basis.
* Highly desirable but not obligatory for completion of supporting documentation

**D. Adjudication Procedures**

The Committee will receive information regarding all heart failure events from the CDC where the supporting documentation will be reviewed for completeness and then forwarded to the HFEC.

The CDC will submit cases to the HFEC. Batches will consist of between 15 and 30 potential HR events and all accumulated hospitalizations. Batches will be sent a minimum of monthly even if there is only one or 2 cases and more often if there are more than 30 cases. The HFEC will maintain cases in batches, and return adjudicated results in all cases in a batch within 30 days realizing that some potential events and other hospitalization may be returned for additional documentation and reviewed again with a subsequent batch.

Regardless of the size of the committee, two members of the committee, in addition to the Chairman or his designee, will then review and adjudicate the events within 30 days

of receipt of the documentation from the CDC, provided that sufficient supporting documentation has been received from the enrolling center. If the supporting documentation is not sufficient or non-existent within a 14 working days, the enrolling center coordinator is contacted and the required documents are requested.

Two categories of heart failure events have been established to review. Potential heart failure events that occur in a hospital setting (admissions greater than a calendar date change); or those potential heart failure events that occur in an out-of hospital setting (out-patient). The Committee will review and adjudicate all heart failure events. The Committee will classify each event as either 1) a heart failure event, 2) not a heart failure event, 3) uncertain event or 4) needing additional information.

There will be a limit of one heart failure event for any given hospitalization. For heart failure events occurring in an out-patient setting, another heart failure event will not be considered until 1 month has passed since the onset day of the index out-patient heart failure event. Any outpatient intravenous regimen, given for the purpose of treating heart failure, that is scheduled upon discharge as part of the heart failure in-patient treatment regimen, will not be considered as a heart failure event.

All hospitalizations that include a calendar date change will be reviewed by the Committee to confirm the absence of a heart failure event and then classify each hospitalization as a cardiovascular basis for admission or a non-cardiovascular basis for admission. Each of the cardiovascular hospitalization classifications will be further sub classified and recorded on a specific report form.

**1. Potential Heart Failure Event**: The Chairman will assign two cardiologist members, in addition to himself, for review of each potential HF event. These members of the committee will review all data submitted by the CDC as a potential HF event.

Each assigned committee member will independently review all of the study data forms of each potential HF event, then document the results of their review on the Endpoint Classification Form.

In all cases, each assigned member will submit their initial classification forms to the Chairman. The Chairman will develop the final heart failure event classification form. The final classification form will represent the majority conclusions of the reviewing members.

If the committee determines that the heart failure end-point is not present but the event occurred in a hospitalization, the Chairman will then complete a hospitalization report form and forward to the CDC.

**2. Hospitalization classified with a cardiovascular diagnosis as the primary cause for admission.** Each cardiovascular hospitalization not considered as a potential heart failure event will be reviewed by a single cardiologist member of the committee for

the purpose of confirming the admitting diagnosis and to determine if the hospitalization contained a heart failure event. The member will forward the hospitalization report form with his/her conclusions to the Chairman. If a heart failure event end-point is suspected, the Chairman or his designee will inform the CDC that the case represents a potential Heart Failure Event. All procedures, as outlined above in section D1 for a potential heart failure event, will then be carried out for a final adjudication by the HFEC.

If the individual reviewer considers the diagnosis to be a cardiovascular admission without heart failure, the reviewer will complete the hospitalization report form to classify the admitting cardiovascular diagnosis based on the documentation supplied. Except in an unusual circumstance, such as suspected heart failure event, additional documents will not be requested to assist in this classification. The reviewer will forward the classification form to the Chairman or his designee, who will then forward to the CDC.

The committee will consider any case for discussion at the request of the individual reviewer. If there is a committee deliberation, a majority vote will dictate the final classification.

**3. Hospitalization classified with a non-cardiovascular diagnosis as the primary cause for admission.** Each hospitalization classified as a non-cardiovascular by the individual investigator sites will be initially reviewed by the cardiac nurse member of the committee. The purpose of the review will be to confirm the non-cardiovascular diagnosis. If the admission is suspected to be due to a cardiovascular cause or a heart failure event is suspected, the data will be forwarded to Chairman or his designee for assignment for review as described in above sections D1 or D2.

If the individual reviewer confirms that the diagnosis is a non-cardiovascular admission without heart failure, the reviewer will complete the hospitalization report form and forward to the Chairman. The Chairman or his designee will review the form and forward to the CDC. The committee will consider any case for discussion at the request of the individual reviewer. If there is a committee deliberation, a majority vote will dictate the final classification.

## E. Voting Procedures

The Committee meeting will proceed as long as the Chairman, or his designee, and one other cardiologist member of the committee are present. Only the cardiologist members will review/vote on the heart failure events. However, no vote will be taken without a majority presence of the members, in person or by phone. All votes will be recorded, and a final classification document, indicating the committee's decision, will be completed and signed and dated by the Chairman or his designee.

In the event the committee's numbers are increased, the requirements will remain that a majority of members will be required to be present in person or by telephone for the

committee to proceed with voting. If there is initial agreement on the classification between committee members, the endpoint will be classified accordingly and considered closed. However, if there is disagreement between the team members, the endpoint will go to full committee discussion.

In events initially classified, as needing additional information, the Chairman or his designee will request additional information from the CDC. That study endpoint decision will be tabled and placed on the agenda for review at the next committee meeting, pending the provision of the additional information requested. Tabled events will not be considered for interim analyses. All tabled events will be adjudicated as heart failure, non-heart failure, or uncertain/indeterminate events prior to the final primary endpoint analysis. Those events adjudicated as non-heart failure or uncertain/indeterminate events will not be counted in the final primary endpoint analysis.

A majority of the voting members will determine the classification of the event. In a case where there is a tie in any vote, the Chairman or his designee reserves the right to make the final determination of the case classification. All votes will be recorded and a final Heart Failure Endpoint Classification Form, indicating the committee's decision, will be completed and signed by the Chairman or his designee. Meeting minutes will be provided to the CDC following each meeting.

**F. Study Endpoint Case Report Forms**

The CDC will forward each committee member the appropriate documentation for all potential heart failure events and hospitalizations.

For potential heart failure events, each committee member will independently review and document the results of his/her analysis on the Heart Failure Endpoint Classification Form. The individual reviewer will sign, date and complete staff code entry.

For hospitalizations, a single member review will be carried out and the Hospitalization Classification Form will be completed by the reviewer. The individual reviewer will sign, date and complete staff code entry. Committee members will be responsible for having these forms in hand for in-person or phone conferences.

The Committee Chairman will preside over any discussion of the endpoint and will be responsible for the documentation of the adjudicated outcome. The Chairman will complete a Heart Failure Endpoint Classification Form in the name of the HFEC. Once the adjudication/classification process is complete, The Chairman or his designee will complete, sign and date the Heart Failure Endpoint Classification Form and forward it and the individual review classification forms to the CDC. All hospitalization report forms will be forwarded to the Chairman who will forward them to the CDC

**Mortality Events Review Committee:** Every effort will be made to classify cardiac deaths in terms of suddenness and arrhythmic mechanism by pre-specified Hinkle-Thaler criteria. Operative deaths associated with implantation of the CRT-D and ICD-only devices will be counted as cardiac deaths. Terminal events will be documented by clinical data from the hospital or out-patient record in English, the official language of the study.

Members of the Mortality Events Review Committee are:

Goldstein, Robert E., MD (Chair)
USUHS
Bethesda, MD

Krone, Ronald, MD
Barnes-Jewish Hospital
St. Louis, MO

# Mortality Endpoint Review Committee Operating Manual

**Purpose:**
To outline the procedures to be followed by the Mortality Endpoint Review Committee (MERC) for the adjudication of deaths in the MADIT-CRT trial.

**Scope:**
Classification of deaths according to cause; mechanism; committee composition; preparation of data for committee adjudication; adjudication procedures; documentation of adjudication; mortality case report forms; endpoint documentation and data flow.

**A. Classification of Underlying Cause of Death**
In MADIT-CRT, participant deaths will be categorized according to clinical and laboratory evidence (including imaging studies) gleaned before and during the terminal event and, when available, autopsy reports. The major categories of classification are:

3. Atherosclerotic coronary heart disease
4. Nonischemic cardiomyopathy—the exclusive or preponderant cause
5. Vascular disorders—cerebrovascular disease, pulmonary embolism or systemic embolism
6. Non-cardiovascular disease
7. Unknown or uncertain cause

## 1 B. CLASSIFICATION OF MECHANISM OF DEATH

Similar clinical and laboratory evidence will be analyzed to determine the specific, preponderant mechanism leading to death. Major categories are:

1. Primary arrhythmic death, with or without congestive heart failure (CHF)
2. Primary cardiac pump failure in a progressive, relapsing, or non-progressive pattern
3. Acute coronary syndrome, including acute myocardial infarction and unstable angina
4. Death related to implanted study device
5. Death related to other cardiac procedure
6. Non-cardiac death
7. Unknown or uncertain precipitating factor

Mechanism of death will also be classified according to the modified Hinkle criteria using the same criteria for arrhythmic death, pump failure, and ischemic death. Pump failure will be judged the preponderant cause if study participants exhibit symptoms or signs of severe congestive heart failure as a consistent feature of their clinical course.

Mortality in patients dying with manifestations of severe CHF (e.g., pulmonary edema, cardiogenic shock, or debilitating typical symptoms that are recurrent or persistent at rest) will be attributed to cardiac pump dysfunction even if the terminal episode involves complex events (e.g., hypoxia or hypotension) and multiple disordered organ systems (e.g., kidney, liver, or brain). Cardiogenic shock will not qualify as worsening CHF unless additional, more specific features of CHF are also present. At least 24 hours must pass following randomization and device implantation for a death to be ascribed to CHF. Cardiac death will be defined as mortality preponderantly due to a disease condition of the heart that provides the physiological and anatomical substrate for terminal events. Death will be attributed to the implanted study device if such death is deemed a direct consequence of study device presence or malfunction or the result of procedures to install or maintain the study device. Death will be attributed to "other cardiac procedure" if precipitated by a procedure involving the heart that is not an intrinsic part of the installation or maintenance of the study device, e.g., PCI or cardiac surgery. When crucial evidence is uncertain or unavailable regarding the mechanism of death (cardiac vs. non-cardiac or study device related vs. non-device related), the overall assessment of cause (Form 19B, Item 13) will be "unknown/indeterminate."

**C. Committee Composition**

The MADIT-CRT Mortality Endpoint Review Committee (MERC) will consist of, at a minimum, three non-participating cardiologists. One of the cardiologists specializes in electrophysiology, one is an invasive cardiologist, and one is a non-invasive, general cardiologist. The committee will be responsible for the adjudication of the cause of death in the MADIT-CRT clinical trial participants and will meet quarterly at a minimum. The purpose of this process is to provide maximum uniformity and continuity in the review and categorization of study deaths, while still maintaining latitude for professional judgment by the investigators and committee members. In the event that future additions to the committee would be considered necessary, additions will be purposely made to ensure that the committee will always be composed of an odd number of members.

**The Committee members** are the following:
Robert E. Goldstein, M.D., Uniformed Services University, Bethesda, MD, Chairman
Ronald J. Krone, M.D., Washington University of St. Louis, St. Louis, MO
Mark C.P. Haigney, M.D., Uniformed Services University, Bethesda, MD

## 2 D. PREPARATION OF DATA FOR COMMITTEE ADJUDICATION

The Coordination and Data Center (CDC) will collect, prepare, and ensure that all data will come to the committee without subject identification or any descriptions of device implantation. The CDC will also compile and forward to the MERC the following data for all deaths:

**Supporting Documentation**
Form 19A (completion of the narrative summary required)
Summary of Final Hospital Stay (if applicable)
* Initial History and Physical exam

* Chest X-Ray, echocardiogram, and lab reports from time most proximate to death

Death Certificate
Autopsy Report (if applicable)
Form ENR, Q7-10
Form 3A
Form 5A and B, Q4-7 (last ones completed prior to the event)
Forms 6A, Q4-13 and 12A, Q5-6 (last three prior to death)
Form 10A, Q4-9 (last prior to death)
Forms 14A, 15A, and 15B (referring to events within three months proximate to death)
Form 18A (last prior to death)
Form 30A
Other supporting documents as requested by the committee on a case-by-case basis.
*** Highly desirable but not obligatory for completion of supporting documentation**

**E. Adjudication Procedures**

The Committee will receive information regarding all deaths from the enrolling centers. This information will be first sent to the CDC where the supporting documentation will be reviewed for completeness and then forwarded to the MERC. Regardless of the size of the committee, two members of the committee, in addition to the Chairman, will then review and adjudicate the events within 30 days of receipt of the documentation from the CDC, provided that sufficient supporting documentation has been received from the enrolling center. If the supporting documentation is not sufficient or non-existent within a reasonable period of time, the enrolling center coordinator is contacted and the required documents are requested.

Every member of the committee will review all data submitted by the CDC regarding death of study participants. Each committee member will independently review all of the study data forms for each death then document the results of their review on the Terminal Event Adjudication Form. In all cases, each assigned member will submit initial classification forms to the Chairman. The Chairman will develop the final mortality classification form. The final classification form will represent the majority conclusions of the reviewing members.

**F. Voting Procedures**

The Committee meeting will proceed as long as two of three of the cardiologist members of the committee are present. Only the cardiologist members will review/vote on the mortality events. However, no vote will be taken without the presence of three members, in person or by phone. All votes will be recorded, and a final classification document, indicating the committee's decision, will be completed and signed and dated by the Chairman.

In the event the committee's numbers are increased, the requirements will remain that three members will be required to be present in person or by telephone for the committee

to proceed with voting. If there is initial agreement on the classification between committee members, the endpoint will be classified accordingly and considered closed. However, if there is disagreement between the team members, the endpoint will go to full committee discussion.

In events initially classified as needing additional information, the Chairman will request additional information from the site investigator. The request will be forwarded via the CDC to the site investigator. That study endpoint decision will be tabled and placed on the agenda for review at the next committee meeting, pending the provision of the additional information requested. If with all available additional information, the committee is still unable to classify the event, the event will be adjudicated as unknown**.**

A majority of the voting members will determine the classification of the event. In a case where there is a tie in any vote, the Chairman reserves the right to make the final determination of the case classification. All votes will be recorded and a final Terminal Event Adjudication Form, indicating the committee's decision, will be completed and signed by the Chairman or his designee.

**G. Study Endpoint Case Report Forms**

The CDC will forward each committee member the appropriate documentation for all mortality events. Each committee member will independently review and document the results of his/her analysis on the Terminal Event Adjudication Form. The individual reviewer will sign, date and complete staff code entry. Committee members will be responsible for having these forms in hand for in-person or phone conferences. The Committee Chairman will preside over any discussion of the end-point and will be responsible for the documentation of the adjudicated outcome. The Chairman will complete a Terminal Event Adjudication Form in the name of the MERC. Once the adjudication/classification process is complete, The Chairman or his designee will complete, sign and date the Terminal Event Adjudication Form and forward it and the individual review classification forms to the CDC.